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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

In vitro leishmanicidal activity of lactone 1,4-dihydroquinoline derivatives against *Leishmania (Leishmania) amazonensis*

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Abstract

A series of lactone 1,4-dihydroquinoline derivatives **4** (**4** and **4aa–4cm)** was screened for in vitro antileishmanial activity against the promastigote form of *Leishmania (Leishmania) amazonensis*. Screening results indicate that all of the synthesized compounds significantly reduced the growth of promastigote forms of promastigotes of *L. (L.) amazonensis*. The cytotoxicity of the most active compounds was also measured on peritoneal macrophage cells. Compounds **4ah** and **4bn** showed better activities than other derivatives with IC_{50} values of 6.22 and 9.05 μM, respectively, with selectivity index 22 and 15 times less toxicity to macrophages cells than to parasites, respectively. The experimental data propose that the compounds may be further investigated against amastigote forms and may contribute to the search of new candidates drugs for treatment of cutaneous leishmaniasis.

Keywords Cutaneous leishmaniasis · Dihydroquinoline derivatives · Lactone

Introduction

Leishmaniasis are neglected tropical diseases caused by protozoan parasites of the *Leishmania* genus and transmitted by the bite of female sandfly vectors (Pace 2014). These infections are endemic in 98 countries, with more than 12 million cases, and 350 million people living in an area at risk (Bhutta et al. 2014; Okwor and Uzonna 2016). The expression of leishmaniasis depends on a complex interaction between the type of infecting species and host immune response. Infection may be asymptomatic or may manifest as cutaneous leishmaniasis (CL) that is pleiomorphic in presentation, mucocutaneous leishmaniasis (MCL), or visceral leishmaniasis (VL) that may be lethal if untreated (Desjeux 2004; Pace 2014). In Latin America, *Leishmania (Leishmania) amazonensis* is responsible for a cutaneous diffuse form that in some cases may also result in visceral leishmaniasis (Torres-Guerrero et al. 2017).

The treatment of CL and VL is based on the use of expensive and toxic drugs, and that to a great extent must be administered by the parenteral route. The most used drugs are derivatives of pentavalent antimony; however, in many areas of this disease, parasitic resistance is already widespread (Ponte-Sucre et al. 2017). The second line of treatment is amphotericin B, an antifungal with a broad spectrum of action and that shows a high toxicity in the host (Fernández-García et al. 2017). Its less toxic lipid formulation is extremely expensive and incompatible with treatment in developing countries (Kumar et al. 2009; Pace 2014; Durieu et al. 2016; Fernández-García et al. 2017). Among the other drugs used in leishmaniasis therapy, miltefosine is the first oral treatment against VL, but its teratogenicity excludes the treatment of pregnant women and its slow turnover could promote the emergence of clinical parasite resistance (Singh et al. 2012; Durieu et al. 2016).

Therefore, these factors justify the search for new chemical series in order to find an orally safe and active drug (Loedige 2015; Ashok et al. 2017). The choice of the dihydroquinolinic nucleus associated with the lactonic ring is due to the presence of these pharmacophoric groups in several compounds with important leishmanicidal

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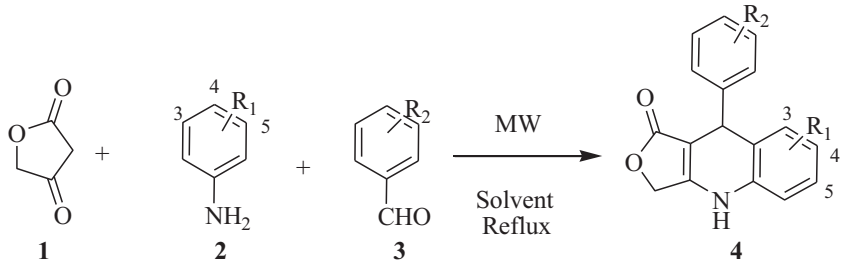
Table 1 Synthesis of dihydroquinoline lactone derivatives **4** and inhibition of the growth of *L. amazonensis* promastigote forms (%)



1 **2** **3** **4**

Entry	Aniline R1	Aldehyde R2	MM	Product	Inhibition (%)
1	**H**	H	261.27	4	64.75 ± 5.75
2	**3,4,5-OCH_3 (2a)**	3,4-(OCH_2O) (**3a**)	395.36	4aa	40.04 ± 6.68
3		3,4-(OCH_3) (**3b**)	411.40	4ab	38.60 ± 4.33
4		3,4,5-OCH_3 (**3c**)	441.43	4ac	79.85 ± 2.59
5		4-Cl (**3d**)	385.80	4ad	77.45 ± 5.05
6		4-Bn, 3-OCH_3 (**3e**)	487.50	4ae	94.96 ± 3.29
7		4-F (**3f**)	369.34	4af	78.89 ± 5.05
8		4-CH_3S (**3g**)	397.44	4ag	92.32 ± 2.72
9		4-CF_3 (**3h**)	419.35	4ah	89.92 ± 4.37
10		6-NO_2-3,4-(OCH_3) (**3i**)	456,40	4ai	50.36 ± 3.29
11		3-OCH_3, 4-OH (**3j**)	397.38	4aj	48.68 ± 2.31
12		3,4-OH (**3m**)	383.35	4am	56.49 ± 0.86
13		6-NO_2-3,4-(OCH_2O) (**3n**)	440.36	4an	100.00 ± 0.00
14	**3,4-(OCH_2O) (2b)**	3,4-(OCH_2O) (**3a**)	349.29	4ba	61.63 ± 5.40
15		3,4-(OCH_3) (3**b**)	365.34	4bb	70.26 ± 11.24
16		3,4,5-OCH_3 (**3c**)	395.36	4bc	64.26 ± 2.90
17		4-Cl (**3d**)	369.76	4bd	50.83 ± 2.90
18		4-Bn, 3-OCH_3 (**3e**)	441.43	4be	79.67 ± 2.45
19		4-F (**3f**)	323.27	4bf	55.15 ± 2.19
20		4-CH_3S (**3g**)	351.38	4bg	16.78 ± 13.97
21		4-CF_3 (**3h**)	373.28	4bh	35.97 ± 2.59
22		6-NO_2-3,4-(OCH_3) (**3i**)	410.33	4bi	100.00 ± 0.00
23		3-OCH_3, 4-OH (**3j**)	351.31	4bj	55.13 ± 3.78
24		6-NO_2-3,4-(OCH_2O) (**3n**)	394.29	4bn	95.99 ± 3.13
25	**3,4-(OCH_3) (3c)**	3,4-(OCH_2O) (**3a**)	365.34	4ca	73.62 ± 7.06
26		3,4-(OCH_3) (3**b**)	381.38	4cb	78.01 ± 2.52
27		3,4,5-OCH_3 (**3c**)	411.40	4cc	72.56 ± 4.21
28		4-Cl (**3d**)	355.77	4cd	100.00 ± 0.00
29		4-Bn, 3-OCH_3 (**3e**)	457.47	4ce	68.82 ± 5.40
30		4-F (**3f**)	339.32	4cf	74.10 ± 2.15
31		4-CH_3S (**3g**)	367.42	4cg	74.10 ± 2.87
32		4-CF_3 (**3h**)	389.32	4ch	100.00 ± 0.00
33		6-NO_2-3,4-(OCH_3) (**3i**)	426.38	4ci	65.23 ± 1.14
34		3,4-OH (**3m**)	353.33	4cm	95.99 ± 2.17
35		6-NO_2-3,4-(OCH_2O) (**3n**)	441.33	4cn	83.96 ± 5.00

properties (Castaño et al. 2009; Reynolds et al. 2013; Coimbra et al. 2016). As part of our ongoing interest on the antiparasitic activity of compounds, we have evaluated herein the leishmanicidal potential of 35 lactone 1,4-dihydroquinoline derivatives against the parasite *L. (L.) amazonensis* in vitro.

Results and discussion

Chemistry

The 1,4-dihydroquinoline lactone derivatives **4** and **4aa–4cm** were obtained in a previous work of our research group from microwave-assisted multicomponent reaction between tetronic acid, aromatic aldehyde, and anilines in ethanol (Table 1). These compounds showed interesting antimicrobial activities against oral bacteria (Laurentiz et al. 2018).

Derivatives **4a–4cn** have three different groups of electron-donating substituents on the dihydroquinolinic ring (3,4,5-OCH_3, 3,4-OCH_2O, and 3,4-OCH_3) and on the benzyl ring with electron-donating or electron-withdrawing substituents: OCH_3, OCH_2O, OH, Cl, CF_3, OBn, F, and NO_2 e SCH_3.

Antileishmanicidal activities

A preliminary screening of 35 lactones 1,4-dihydroquinoline derivatives was performed at 100 µM against promastigote forms de *L. (L.) amazonensis* to select the most active compounds at higher concentrations.

Although the clinically relevant form of the parasite is the amastigote form, which shows metabolic differences from the extracellular forms, promastigotes can be used for fast screenings of potential compounds (Tempone et al. 2005; Martín-Montes et al. 2017; Silva et al. 2017). Thus, in this study, we evaluated the effect of dihydroquinoline lactone derivatives against promastigote forms of *L. (L.) amazonesis* in vitro.

The compounds **4aa, 4ab, 4aj, 4bg**, and **4bh** showed a percentage of inhibition of cell growth of less than 50% at 24 h (Table 1). The other compounds showing activity higher than 50% include the unsubstituted compound **4**, however, only those with activity greater than 80% were submitted to additional assays in lower concentrations. Among the compounds with parasite activity above 80%, it was possible to observe that the compounds containing the nitro piperonal group as a substituent on the benzyl ring, independent of the substituent of the quinolinic moiety, are among the most active compounds (**4an**, **4bn**, and **4cn**). Compounds **4ah** and **4ch** containing the CF_3 group were also very active at this concentration.

Table 2 In vitro leishmanicidal activity: IC_{50}, CC_{50}, and selectivity index for dihydroquinolinine lactone derivatives

Compounds	Promastigote forms	Peritoneal macrophages	
	IC_{50} µM[a]	CC_{50} µM[b]	SI
4ae	5.29	6.07	1.13
4ag	32.5	ND	–
4ah	6.22	139.20	22.31
4an	33.40	ND	–
4bi	2.62	13.90	5.03
4bn	9.05	136.27	15.05
4cd	22.09	ND	–
4ch	17.90	ND	–
4cm	73.50	ND	–
4cn	42.90	ND	–
Amphotericin B	0.65	0.49	0.75

ND not determined, *SI* selectivity index

[a]Inhibition concentration 50 (IC_{50}) values were calculated using a nonlinear regression curve

[b]Cytotoxic concentration 50 (CC_{50}) values were calculated using a nonlinear regression curve

[c]SI was calculated from the ratio of CC_{50} values of macrophage and IC_{50} promastigotes

The substitution on phenyl and dihydroquinoline rings had a considerable effect on potency of other derivatives in comparison with unsubstituted compound **4**. All the evaluated compounds inhibited the growth of *L. (L.) amazonensis* promastigote forms to a greater or lesser degree, however, only those compounds that presented reduction on growth inhibition of promastigote forms with a percentage above 80% were evaluated at concentrations of 1.00–100 µM (Table 2).

According to hit-and-lead criteria, a hit compound should demonstrate $IC_{50} < 10$ µM against protozoan parasites and a selectivity index greater than 10-fold between the half-maximal cytotoxic concentration (CC_{50}) for the mammalian cell line and the IC_{50} for parasite (Dardonville et al. 2009; Katsuno et al. 2015). In this study, in promastigote activity assay at lower concentrations, the reported lactones 1,4-dihydroquinoline, displayed the growth of *L. (L.) amazonensis* promastigote forms with IC_{50} value ranges of 2.62–73.50 µM (Table 2). Among the reported compounds, analogs **4ae**, **4ah**, **4bi**, and **4bn** were more potent in inhibiting the *L.(L.) amazonensis* promastigotes with IC_{50} values of 5.29, 6.22, 2.62, and 9.05 µM, respectively. The positive control, amphotericin B, displayed the growth of the *L.(L.) amazonensis* promastigote forms with an IC_{50} value of 0.65 µM.

Among the compounds containing R1 = 3,4,5-OCH_3, **4ae** and **4ah** were more active with IC_{50} values of 5.29 and 6.22 µM, respectively. Compound **4ae** has electron donor

substituents in *para* (OBn) and *meta* (OCH_3) positions, while compound **4ah** has a single electron-withdrawing substituent in *para* (CF_3) position. The change of the OBn group for CF_3 and OCH_3 groups for H resulted in a small loss of activity, but contributed to enhance the selectivity index of **4ah** by almost 20x in relation to **4ae**. The nature of R2 and the degree of substitution for these two compounds mainly affected the selectivity index, showing that the hydrophobic and electronegative character of the CF3 group in addition to their smaller size contributed to the higher selectivity of **4ah** on *L. (L.) amazonensis* promastigote forms. The compounds more active with $R1 = OCH_2O$ were **4bi** and **4bn** that have in common the nitro group connected to the phenyl ring. The presence of two OCH_3 groups on the phenyl ring (R2) contributes to the increase of **4bi** activity in relation to **4bn**, which presents the methylenedioxy group in the same position. These two groups of substituents in R2 have an electron donor character; however, the methylenedioxy group presents a more rigid character because it is a cycle and also has a greater hydrophobic character. Compound **4bi** showed better activity ($IC_{50} = 2.62$ μM, SI = 5.03), however, it was about three times less selective than **4bn** ($IC_{50} = 9.05$ μM, SI = 15.05).

The compounds containing the 3,4-dimethoxy substituents on the 1,4-dihydroquinolinic moiety were the least active (**4cd**, **4ch**, **4cm**, **and 4cn** with $IC_{50} > 17$ μM) independently of a substituent on the phenyl ring, however, these substituents on the dihydroquinolinic ring are not favorable to the leishmanicidal activity for this class of compounds.

Thus, the compounds with IC_{50} values below 10.0 μM (Table 2) are those with 3,4,5-trimethoxy and 3,4-methylenedioxy substituents in the 1,4,-dihydroquinolinic moiety, i.e., these groups are favorable to the action of this class of compounds and, therefore, the choice of the substituent on the benzyl ring is determinant for the increase in leishmanicidal activity.

Regarding macrophage cytotoxicity, the less toxic compounds were **4ah** and **4bn** with CC_{50} values of 139.20 and 136.27 μM, respectively. Compound **4bi** was one of the most toxic, as well as **4ae**, respectively, with CC_{50} values of 13.9 and 6.07 μM. In relation to the selectivity index, **4ah** and **4bn** were, respectively, 22 and 15 times less toxic to macrophage cells than the control amphotericin B that showed SI = 0.75 (Table 2).

The presence of the nitro group allied to the methylenedioxy group on the benzylic ring in **4bn** increased the selectivity index, as evidenced by the much lower selectivity index of the compound **4bi**. The presence of the CF_3 group in **4ah**, smaller and more lipophilic, favored the increase of the selectivity index when compared to **4ae** that has the OCH_3 and OBn groups on the phenyl ring.

Our results demonstrate the importance of the 1,4-dihydroquinolinic nucleus in the study of compounds with antileishmanial properties. Recent works have confirmed the interesting antileishmanial properties of quinoline derivatives (Antinarelli et al. 2015; Herrera et al. 2016; Navneetha et al. 2017). In these works, various quinoline derivatives have been synthesized and showed results that attest to the importance of this pharmacophore nucleus for leishmanicidal activity against the promastigote form. However, few studies report the activity of 1,4-dihydroquinoline derivatives, which demonstrates that the potential of this class of compounds has not yet been adequately explored.

Conclusion

Thirty-five lactone 1,4-dihydroquinoline derivatives were submitted to antileishmanial assay against promastigote forms of *L. (L.) amazonesis* in vitro. Among the evaluated compounds, **4ah** and **4bn** showed promising in vitro antileishmanial activity and low toxicity in macrophage cells. These compounds are interesting targets that emerge among the various classes of compounds already synthesized and evaluated against leishmaniasis. The results obtained with these compounds are an additive justification for further studies of the lactone 1,4-dihydroquinoline derivatives against amastigote forms and may contribute to the search for new molecules as targets for the development of more potent and fewer side-effect drugs.

Materials and methods

Chemistry

A mixture of tetronic acid (1.0 mmol), benzaldehydes (1.0 mmol), and anilines (1.0 mmol) in ethanol (2 mL) was taken in a reaction flask equipped with a small magnetic stirring bar and the reflux condenser. The mixture was then irradiated in a microwave reactor for 15 min (reflux temperature of the solvent) at a power of 200 W. After the reaction was complete (TLC monitoring), the mixture was then cooled to room temperature and the solvent was removed on rotary evaporator. The precipitated crude product was washed with a mixture of hexane-ethyl acetate (8:2) and dried under vacuum. The variation of anilines (**2a–c**) and benzaldehydes (**3a–n**) furnished the lactone 1,4-dihydroquinolines **4aa**–**4cn** in yields ranging from 69 to 92%. Data of characterization of the compounds were described by Laurentiz et al. (2018).

Biological assays

Antileishmanial activity

Cultures of *L. (L.) amazonensis* (MHOM/BR/PH8) promastigote forms were maintained at 25 °C in RPMI 1640 medium (Gibco) supplemented with 10% fetal bovine serum (FBS, Cultilab), 50 units·mL^{-1} penicillin, and 50 mg·mL^{-1} streptomycin (Cultilab).

The initial screening was assessed in vitro by cultivating *L. (L.) amazonensis* promastigotes (1×10^6 parasites mL^{-1}) in a 96-well plate containing RPMI 1640 medium (Gibco) supplemented with 10% FBS (Cultilab), 50 units·mL^{-1} penicillin, and 50 mg·mL^{-1} streptomycin (Cultilab) in the presence of 100 µM of compounds previously dissolved in 100% dimethylsulfoxide (DMSO) (Synth). Cultures were incubated at 25 °C in BOD (Quimis) for 24 h and the leishmanicidal activity was determined by growth inhibition of promastigote forms by counting the total number of live promastigotes in the Neubauer chamber (Global Glass), considering flagellar motility (Azzouz et al. 2005).

The compounds that showed greater than or equal to 80% inhibition of cell growth during 24 h were evaluated at concentrations of 1.00–100 µM. RPMI 1640 medium (Gibco) containing 0.5% DMSO (Synth) (highest concentration) was used as a negative control and amphotericin B (Eurofarma) at concentrations of 0.20–3.37 µM was used as a positive control. Two experiments were performed in triplicate and repeated twice. Determination of 50% inhibition concentration values (IC_{50}) was carried out by GraphPad Prism version 5.0 Windows software (GraphPad Software, USA) using a nonlinear regression model of variable slope.

Macrophages and cytotoxicity assay

Thioglycolate-elicited peritoneal macrophages were obtained from BALB/c mice (weighing 20–25 g) by injection of 500 µL of 3% thioglycolate 3 days prior to peritoneal lavage with 5 mL of ice-cold phosphate- buffered saline (PBS 1 ×). The peritoneal exudate cells were centrifuged at 400 × g for 10 min at 4 °C, the supernatant was removed, and RPMI 1640 (Gibco) medium was supplemented with 10% FBS (Cultilab), 50 units·mL^{-1} penicillin, and 50 mg·mL^{-1} streptomycin (Cultilab) was added to the pellet (macrophages) (Toledo et al. 2014). The experiment was authorized by the University of Franca´s Ethics Committee for Animal Care (approval number: 046/15).

Macrophages (2×10^5 cells/well) were seeded in a 96-well microtiter plate and incubated at 37 °C in a 5% CO_2 atmosphere for 24 h and when the macrophages had developed a monolayer, the cells were exposed with the compounds at concentrations of 1.60 to 200 µM (**4ae, 4ah, 4bi, and 4bn**) or 0.20–3.38 µM (amphotericin B) for 24 h. The morphological changes of treated and untreated cell lines (control) were compared by monitoring, using an inverted microscope (Axio Vert, Carl Zeiss). Cell viability was determined using the vital stain Trypan Blue (Aldrich) at 0.1% concentration in phosphate buffer (Mesa-Valle et al. 1996). The number of dead cells was recorded, and the percentage of viability was determined as [no. of viable cells in the cells treated/no. of viable cells in the cells not treated (negative control)] × 100. RPMI 1640 medium (Gibco) containing 0.5% DMSO (Synth) (highest concentration) was used as a negative control and 25% DMSO was used as a positive control. Two experiments were performed in triplicate and repeated twice. Determination of 50% cytotoxic concentration values (CC_{50}) was carried out by GraphPad Prism version 5.0 Windows software (GraphPad software, USA) using a nonlinear regression model of variable slope.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Antinarelli LMR, Dias RM, Souza IQ, Lima WP, Gameiro J, da Silva AD, Coimbra ES (2015) 4-Aminoquinoline RMP Derivatives as potential antileishmanial agents. Chem Biol Drug Des 86 (4):704–714

Ashok P, Chander S, Chow LMC, Wong ILK, Singh RP, Jha PN, Sankaranarayanan M (2017) Synthesis and in-vitro anti-leishmanial activity of (4-arylpiperazin-1-yl) (1-(thiophen-2-yl)-9H-pyrido[3,4-b]indol-3-yl)methanone derivatives. Bioorg Chem 70:100–106

Azzouz S, Maache M, Garcia RG, Osuna A (2005) Leishmanicidal activity of edelfosine, miltefosine and ilmofosine. Basic Clin Pharmacol Toxicol 96(1):60–65

Bhutta ZA, Sommerfeld J, Lassi ZS, Salam RA, Das JK (2014) Global burden, distribution, and interventions for infectious diseases of poverty. Infect Dis Poverty 3:21–28

Castaño M, Cardona W, Quiñones W, Robledo S, Echeverri F (2009) Leishmanicidal activity of aliphatic and aromatic lactones: correlation structure-activity. Molecules 14(7):2491–2500

Coimbra ES, Antinarelli LM, Silva NP, Souza IO, Meinel RS, Rocha MN, Soares RP, da Silva AD (2016) Quinoline derivatives: synthesis, leishmanicidal activity and involvement of mitochondrial oxidative stress as mechanism of action. Chem Biol Interact 260:50–57

Dardonville C, Fernández-Fernández C, Gibbons SL, Jagerovic N, Nieto L, Ryan G, Kaiser M, Brun R (2009) Antiprotozoal activity of 1-phenethyl-4-aminopiperidine derivatives. Antimicrob Agents Chemother 53(9):3815–3821

Desjeux P (2004) Leishmaniasis: current situation and new perspectives. Comp Immunol Microbiol Infect Dis 27(5):305–318

Durieu E, Prina E, Leclercq O, Oumata N, Gaboriaud-Kolar N, Vougogiannopoulou K, Aulner N, Defontaine A, No JH, Ruchaud S, Skaltsounis AL, Galons H, Späth GF, Meijer L, Rachidi N (2016) From drug screening to target deconvolution: a target-based drug discovery pipeline using leishmania casein kinase 1 isoform 2 to identify compounds with antileishmanial activity. Antimicrob Agents Chemother 60(5):2822–2833

Fernández-García R, De Pablo E, Ballesteros MP, Serrano DR (2017) Unmet clinical needs in the treatment of systemic fungal infections: the role of amphotericin B and drug targeting. Int J Pharm 525(1):139–148

Herrera L, Stephens DE, D'Avila A, George KG, Arman H, Zhang Y, Perry G, Leonart R, Larionov OV, Fernández PL (2016) Insights into the structural patterns of the antileishmanial activity of bi- and tricyclic N-heterocycles. Org Biomol Chem 14 (29):7053–7060

Katsuno K, Burrows JN, Duncan K, Huijsduijnen RH, Kaneko T, Kita K, Mowbray CE, Schmatz D, Warner P, Slingsby BT (2015) Hit and lead criteria in drug discovery for infectious diseases of the developing world. Drug Discov 14:751–758

Kumar D, Kulshrestha A, Singh R, Salotra P (2009) *In vitro* susceptibility of field isolates of leishmania donovani to miltefosine and amphotericin B: correlation with sodium antimony gluconate susceptibility and implications for treatment in areas of endemicity. Antimicrob Agents Chemother 53(2):835–838

Laurentiz RS, Gomes WP, Pissurno APR, Santos FA, Santos VCO, Martins CHG (2018) Synthesis and antibacterial activity of new lactone 1,4-dihydroquinoline derivatives. Med Chem Res 27 (4):1074–1084

Loedige M (2015) Design and synthesis of novel antileishmanial compounds. Int J Med Chem 302723:21

Martín-Montes A, Ballesteros-Garrido R, Martín-Escolano R, Marín C, Guitiérrez-Sánchez R, Abarca B, Ballesteros R, Sanchez-Moreno M (2017) Synthesis and in vitro leishmanicidal activity of novel [1,2,3]triazolo[1,5-a]pyridine salts. RSC Adv 7:15715–15726

Mesa-Valle CM, Castilla-Calvente J, Sanchez- Moreno M, Moraleda-Lindez V, Barbe J, Osuna A (1996) Activity and mode of action of acridine compounds against Leishmania donovani. Antimicrob Agents Chemother 40(3):684–690

Navneetha O, Deepthi K, Rao AM, Jyostna TS (2017) A review on chemotherapeutic activities of quinoline international journal of pharmaceutical. Chem Biol Sci 7(4):364–372

Okwor I, Uzonna J (2016) Social and economic burden of human leishmaniasis. Am J Trop Med Hyg 94(3):489–493

Pace D (2014) Leishmaniasis. J Infect 69(Suppl 1):S10–8

Ponte-Sucre A, Gamarro F, Dujardin JC, Barrett MP, López-Vélez R, García-Hernández R, Pountain AW, Mwenechanya R, Papadopoulou B (2017) Drug resistance and treatment failure in leishmaniasis: a 21st century challenge PLoS Negl Trop Dis 11(12): e0006052

Reynolds KA, Loghlin WA, Young DJ (2013) Quinolines as chemotherapeutic agents for leishmaniasis. Mini Rev Med Chem 13 (5):730–743

Silva ARST, Scher R, Santos FV, Ferreira SR, Cavalcanti SCH, Correa CB, Bueno LL, Alves RJ, Souza DP, Fujiwara RT, Dolabella SS (2017) Leishmanicidal activity and structure-activity relationships of essential oil constituents. Molecules 22 (5):815. https://doi.org/10.3390/molecules22050815

Singh N, Kumar M, Singh RK (2012) Leishmaniasis: current status of available drugs and new potential drug targets. Asian Pac J Trop Med 5:485–497

Toledo JS, Ambrósio SR, Borges CH, Manfrim V, Cerri DG, Cruz AK, Da Costa FB (2014) *In vitro* leishmanicidal activities of sesquiterpene lactones from *Tithonia diversifolia* against *Leishmania braziliensis* promastigotes and amastigotes. Molecules 19 (5):6070–6079

Tempone AG, Treiger Borborema SE, Andrade Jr HF, Amorim Gualda NC, Yogi A, Salerno Carvalho C (2005) Antiprotozoal activity of Brazilian plant extracts from isoquinoline alkaloid-producing families. Basic Clin Pharmacol Toxicol 96(1):60–65

Torres-Guerrero E, Quintanilla-Cedillo MR, Ruiz-Esmenjaud J, Arenas R (2017) Leishmaniasis: a review. F1000Res 6:750. https://doi.org/10.12688/f1000research.11120.1